

PORTAL AND PANCREATIC VEIN CATHETERIZATION WITH RADIOIMMUNOLOGIC DETERMINATION OF INSULIN

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HYPOLYCEMIA is caused by pancreatic and extra-pancreatic factors. Extrapaneatic factors causing hypoglycemia are nonendocrine lesions, such as mesodermal tumors, carcinoma of the adrenal cortex, primary carcinoma of the liver, a few carcinomas of the gastrointestinal tract, extensive liver disease and hypofunction of the anterior pituitary and the adrenal cortex. Ninety per cent of the beta cell tumors of the pancreas producing insulin are benign, and 10 per cent are malignant. Metastases are seen in most of the malignant tumors. The tumors are localized in various parts of the pancreas and occasionally may be found outside the pancreas. There may be a single tumor, multiple tumors or diffuse beta cell hyperplasia. Many diagnostic tests reveal the cause of hypoglycemia. Extrapaneatic tumors usually have normal immunoreactive insulin concentrations while pancreatic tumors usually have been diagnosed by high levels of immunoreactive insulin or proinsulin or both in peripheral blood. Insulin determinations are often helpful in diagnosis especially if the insulin levels are related to the blood glucose levels from the sample, higher insulin levels than expected for the level of blood glucose. The only cure, surgical resection, may be technically difficult if the localization of the tumor is unknown, if the hyperinsulinism is caused by insular hyperplasia or if metastases are present. When confronted with a patient with suspected islet cell tumor, it is important to determine preoperatively the localization and number of primary tumors as well as the presence and localization of metastases. Postoperatively, it is important to have a good method for checking the success of the operation, to control the growth of the tumor left in the gland or to diagnose and localize recurrences as early as possible.

Since the first report by Olsson (8) of an angiographically diagnosed insulinoma, arteriography has been considered the most valuable method for preoperative localization of an insulinoma in the pancreas. Many instances are later reported, but

the accuracy of the diagnostic procedure has varied. The preoperative localization was correctly made in seven of eight patients by Boijesen and Samuelsson (1) and in eight of 11 by Deininger (2). Madsen and Hansen (7) found nine insulinomas in 11 patients with three false-positive diagnoses. Robins and his colleagues (9) had an accuracy of 38 per cent, and Gray and his co-workers (5), who reviewed the literature, found an accuracy rate of 63 per cent when comparison was made of positive and negative findings.

The technique for selective catheterization of the portal vein system and the pancreatic veins (Fig. 1) has previously been reported by Göthlin and his colleagues (4), who suggested the method be used in the diagnosis of endocrine tumors of the pancreas, and by Lunderquist and Vang (6).

Peroperative visual identification of an insulinoma using methylene blue infusion during the operation has been reported by Gordon and his associates (3) but cannot be used as a preoperative method.

We (4, 6) have used the technique of selective catheterization of the portal vein system along with simultaneous catheterization of the aortic and caval branches. Blood samples were withdrawn from different branches at the same moment in the three different vessel systems for radioimmunologic determination of insulin. By comparing the values of the simultaneous blood samples, conclusions about the correct diagnosis is theoretically possible, and in our study, a single tumor localization was correctly suggested by the samples.

MATERIALS AND METHOD

Six patients, four women and two men aged 34 to 61 years, have been investigated. One of the female patients, aged 61 years, had hypoglycemic attacks characteristically recognized as Whipple's triad. One patient had duodenal ulceration, three had the Zollinger-Ellison syndrome and one was investigated because of extrathyroid calcitonin production.

With local anesthesia, percutaneous transhepatic

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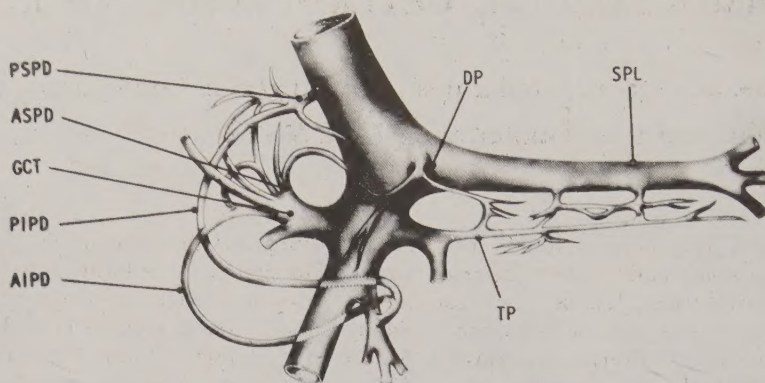


FIG. 1. Venous anatomy of the pancreas. PSPD, Posterior superior pancreaticoduodenal vein. ASPD, Anterior superior pancreaticoduodenal vein. GCT, Gastrocolic trunk. PIPD, Posterior inferior pancreaticoduodenal vein. AIPD, Anterior inferior pancreaticoduodenal vein. TP, Transverse pancreatic vein. DP, Dorsal pancreatic vein. SPL, Splenic vein.

1. v. lienalis	= 37	v. hep = 0	a. coel = 0
2. v. lienalis	= 9	v. hep = 0	a. coel = 0
3. GCT	= 0		
4. v. portae	= 11	v. hep = 18	a. coel = 11
5. v. mes sup	= 0		
6. v. ASPD	= 0		
7. v. portae	= 0		

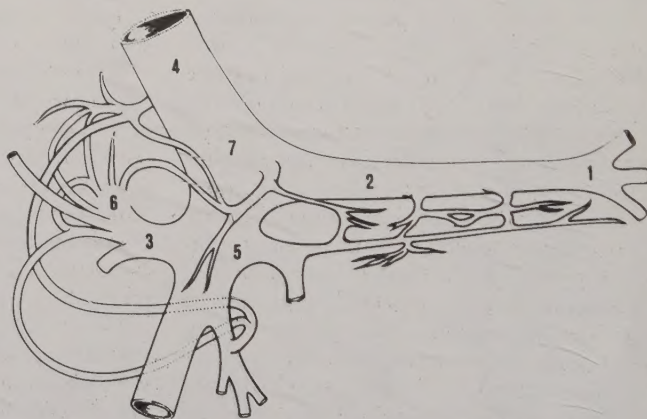


FIG. 2. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 1 without insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

catheterization of the portal vein was performed. At the same time, percutaneous catheterization of the aorta and the vena cava was performed through the femoral artery and vein. A test injection of contrast medium confirmed the correct positioning of the catheters. After knowing the anatomy of the vascular system, blood samples were withdrawn simultaneously from different branches in the three vessel systems. Blood samples were centrifuged and serums stored at -20 degrees C. until radioimmunologic determination of insulin was performed.

Radioimmunologic determination of insulin in the serum was performed using ^{125}I labeled pig

insulin and guinea pig antipig insulin. Insulin standard or unknown sample and antiserum were pipetted into a small glass tube, mixed and incubated for 20 hours at 4 degrees C. ^{125}I labeled insulin was added, mixed and incubated for four hours at 4 degrees C. Thereafter, 96 per cent alcohol was added, and the solution was centrifuged for 20 minutes at 2,000 times gravity. The supernatant was pipetted into a plastic tube which was stoppered, and the radioactivity was counted. After plotting the standard curve counts per minute versus the insulin concentration, the unknown insulin concentration was read.

1. v. lienalis = 28	v. hep = 22
	a. coel = 24
2. v. lienalis = 34	v. hep = 1
	a. coel = 3
3. v. mes inf = 1	v. hep = 1
	a. coel = 0
4. v. lienalis = 14	v. hep = 0
	a. coel = 0
5. v. coronar = 0	v. hep = 1
	a. coel = 0
6. v. PSPD = 11	v. hep = 2
	a. coel = 0
7. GCT = 0	v. hep = 0
	a. coel = 0
8. v. mes sup = 1	v. hep = 5
	a. coel = 0
9. v. ASPD = 0	v. hep = 0
	a. coel = 0
10. v. portae = 4	v. hep = 1
	a. coel = 0

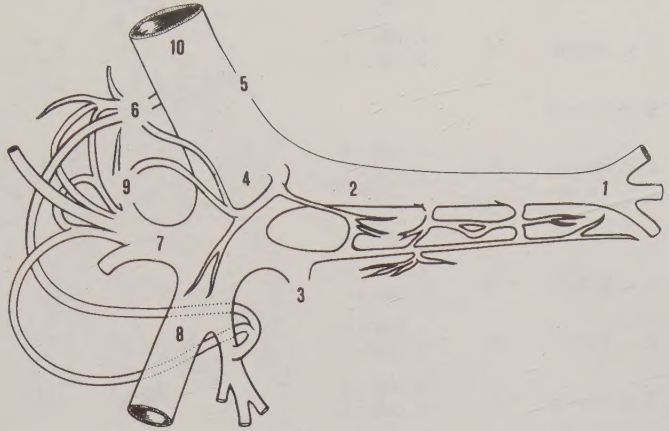


FIG. 3. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 2 without insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

1. v. lienalis = 10	v. hep = 16
	a. coel = 13
2. v. lienalis = 92	
3. v. mes inf = 13	
4. v. jejunal = 5	
5. v. mes sup = 18	
6. v. portae = 26	v. hep = 15
	a. coel = 12

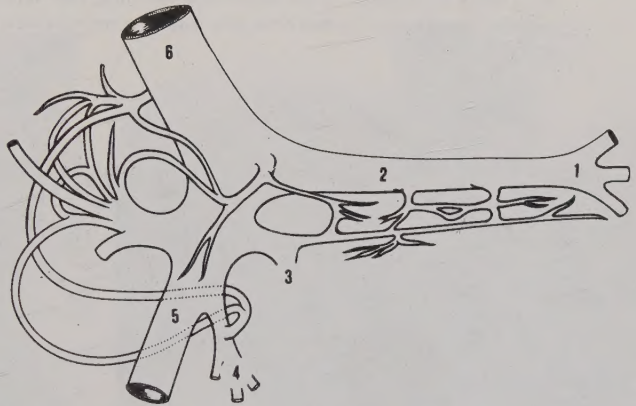


FIG. 4. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 3 without insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

RESULTS

Five of the patients showed normal but variable insulin levels in the peripheral as well as in the portal blood (Figs. 2, 3, 4, 5 and 6). The variation of insulin levels in peripheral blood was small and can be explained by the method. The variation in portal blood could be explained by the distance between the tip of the catheter and draining pancreatic veins. One patient, a woman aged 61 years, had high insulin levels in the peripheral blood. In the portal system, her insulin levels were high but extremely so in the medial portion of the splenic

vein (Fig. 7). Arteriography was performed with selective injection of contrast medium into the gastroduodenal artery showing a normal head and body of the pancreas. Selective injection of the splenic artery showed a large cyst caudal to the spleen and lateral to the tail of the pancreas which was displaced medially. In the tail of the pancreas, a 4 by 5 centimeter hypervascular tumor was found (Fig. 8). The cyst compressed one of the pancreatic veins draining the tail of the pancreas (Fig. 9). The cyst was punctured transabdominally, drained and then filled with contrast medium. It was then pos-

1. v. lienalis	= 4	v. hep = 8	a. coel = 5
2. v. lienalis	= 26	v. hep = 3	a. coel = 1
3. (hemolysis)			
4. v. lienalis	= 31	v. hep = 8	a. coel = 2
5. v. lienalis	= 5	v. hep = 4	a. coel = 2
6. v. portae	= 6	v. hep = 3	a. coel = 2
7. v. PSPD	= 40	v. hep = 4	a. coel = 2
8. v. mes sup	= 11	v. hep = 3	a. coel = 1
9. v. mes sup	= 9		
10. v. mes sup	= 9		
11. v. portae	= 9	v. hep = 1	a. coel = 0

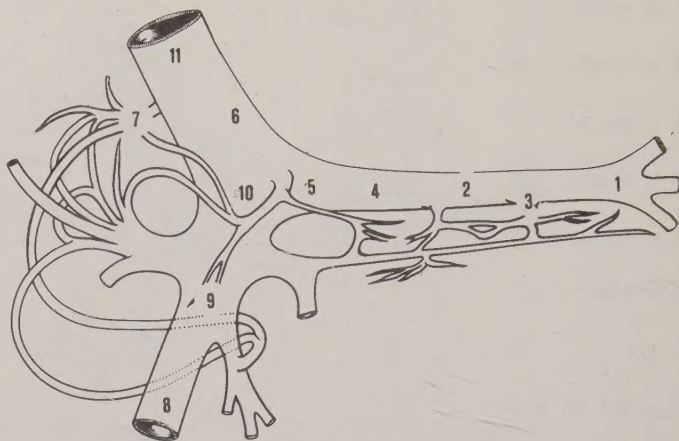


FIG. 5. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 4 without insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

1. v. lienalis	= 0	v. hep = 0
2. v. lienalis	= 0	v. hep = 1
3. v. lienalis	= 0	v. hep = 1
4. v. lienalis	= 12	v. hep = 1
5. GCT	= 2	v. hep = 0
6. v. portae	= 0	v. hep = 3
7. v. jejunal	= 0	

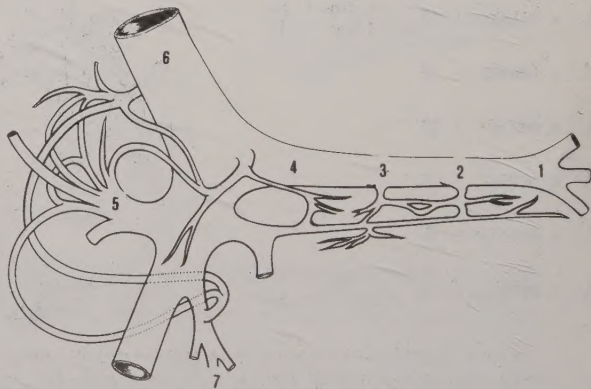


FIG. 6. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 5 without insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

sible to take a transabdominal fine needle biopsy from the tumor in the tail of the pancreas. Cytologic and immunohistologic analysis showed an insulin producing tumor. At operation, it was confirmed that a pancreatic cyst did occlude the pancreatic vein which drained the distal part of the tail to the splenic vein and that the dilated veins from the tumor drained to the middle part of the splenic vein. Resection of the tail of the pancreas was performed. The specimen contained

a 3 by 4 centimeter insulinoma. Palpation of the rest of the pancreas revealed that there was no abnormality.

Postoperatively, the patient underwent reinvestigation in the same manner, and her insulin levels were normal in the portal vein as well as in the peripheral blood (Fig. 10). However, sample number seven taken from the dorsal pancreatic vein (Fig. 11) had 99 microunits of immunoreactive insulin per milliliter of serum and sample number

1. v. lienalis	= 112	v. hep = 91 a. coel = 113
2. v. lienalis	= 95	v. hep = 97 a. coel = 106
3. v. lienalis	= 704	v. hep = 93 a. coel = 99
4. v. portae	= 211	v. hep = 88 a. coel = 83
5. v. gastroepipl. dx	= 91	v. hep = 101 a. coel = 140
6. v. mes. sup	= 108	v. hep = 115 a. coel = 259
7. v. ASPD	= 304	v. hep = 132 a. coel = 129
8. GCT	= 101	v. hep = 81 a. coel = 156
9. v. mes inf	= 157	v. hep = 167 a. coel = 179
10. v. portae	= 327	v. hep = 174 a. coel = 163

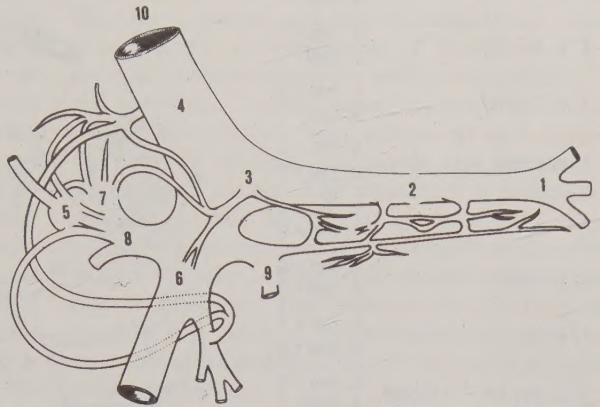


FIG. 7. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from the hepatic vein and celiac artery of Patient 6 with insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.



FIG. 8

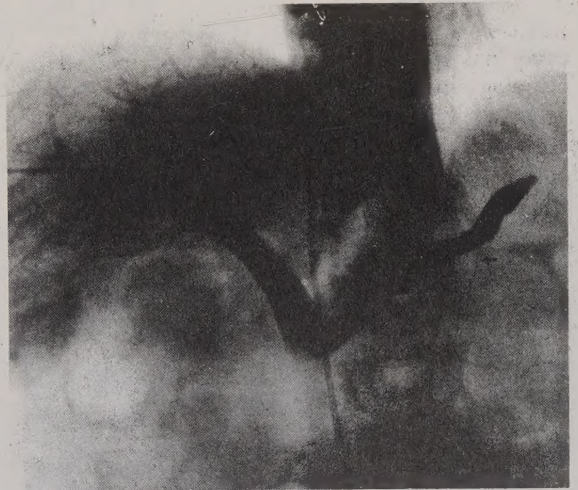


FIG. 9

FIG. 8. Selective injection into the splenic artery reveals an 11 centimeter cystic lesion caudal to the spleen which is displaced upwards and lateral to the tail of the pancreas which is displaced medial and downwards. In the tail of the pancreas is a 4 by 5 centimeter hypervascular tumor.

FIG. 9. Percutaneous, transhepatic catheterization of the portal vein and injection of contrast medium into the splenic vein. Pancreatic vein compressed by the cystic lesion, arrow.

one from the anterior superior pancreaticoduodenal vein had 200 microunits. Follow-up studies will tell if this is a sign of a residual tumor or of a second pancreatic tumor not found at operation or if it is a normal value for a pancreatic vein. The percutaneous transhepatic catheterization of the

portal vein and its branches was performed without any side-effect or complication in all patients.

DISCUSSION

The ideal method for measuring insulin in the blood has not yet been developed. Radioimmuno-

1. v. ASPD	= 200	v. hep = 7 a. coel = 4
2. v. mes sup	= 1	v. hep = 3 a. coel = 0
3. v. lienalis	= 5	v. hep = 6 a. coel = 7
4. v. portae	= 0	v. hep = 0 a. coel = 3
5. v. PSPD	= 0	v. hep = 1 a. coel = 0
6. v. portae	= 9	v. hep = 0 a. coel = 0
7. v. DP	= 99	v. hep = 1 a. coel = 0
8. v. mes inf	= missed	v. hep = 3 a. coel = 1
9. v. jejunal	= 0	v. hep = 0 a. coel = 1
10. GCT	= missed	v. hep = 2 a. coel = 1
11. v. mes sup	= 0	

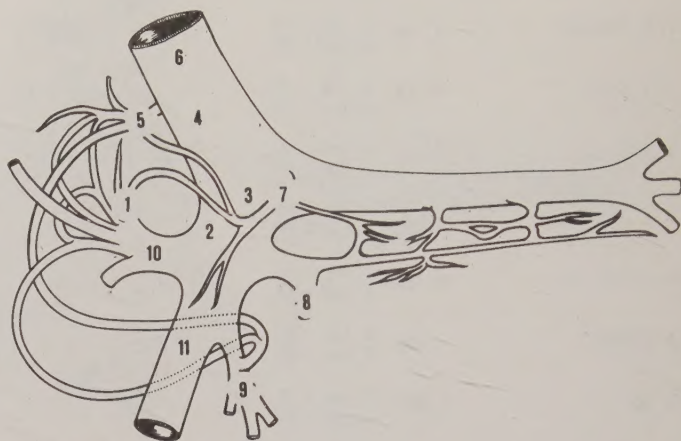


FIG. 10. Localization of portal vein blood samples and the immunoreactive insulin values compared with those withdrawn at the same moment from Patient 6 after caudal hemipancreatectomy because of an insulinoma. Immunoreactive insulin concentrations expressed in microunits per milliliter of serum.

assay has made an explosive impact upon endocrinology in the past decade. The insulin assay is generally regarded as one of the most accurate. However, interassay and intraassay variations are

often large even in the best laboratories. The insulin concentration in peripheral blood is in fasting, nonobese normal persons between 10 and 20 microunits per milliliter. High carbohydrate meal and glucagon may raise the concentration to about 150 to 250 microunits per milliliter.

We have studied immunoreactive insulin concentrations in the vena cava, aorta and portal vein in six fasting patients, one of whom had clinical signs of insulinoma. The five patients without insulinoma had variable low immunoreactive insulin concentrations in all vessel systems compared with the values found in the patient with signs of insulinoma. The concentrations of immunoreactive insulin in samples taken simultaneously at different localizations may be comparable and indicate vessels draining tumor areas (Fig. 10 compared with Fig. 7). Administration of an insulin releasing agent may increase the possibility of finding small insulin releasing tumors. This was not performed during the present investigation. More proinsulin is released from islet cell tumors than from the islet cells in a normal pancreas. Proinsulin has not been determined in our patients.

There are many known hormone producing tumors. When possible, hormonal determination should be used to improve the preoperative diagnosis as well as for the postoperative or postmedical



FIG. 11. Selective catheterization of the dorsal pancreatic vein.

follow-up examination. For instance, patients suspected of having a gastrinoma or G cell hyperplasia causing recurrent duodenal ulcers may be evaluated by hormonal determination of venous samples drawn from the portal system including the coronary and pancreatic veins. The hormone determinations combined with gastroscopic biopsy may reveal or exclude G cell hyperplasia or gastrinomas. With appropriate catheterization, hepatic metastases as well as lymphatic metastases may be revealed. Carcinoids could be preoperatively localized through catheterization of the portal vein and its branches. The extent of operative procedures can be decided after radiologic and immunologic diagnoses, and recurrences could be detected earlier when the procedure is used as a part of the follow-up study. Paraendocrine hormone producing tumors may be localized by this method. Multiple hormonal determination of samples from different veins instead of the single hormone determination may reveal multiple hormone producing tumors.

By sampling from different hepatic veins, hormone producing metastases could be carefully localized preoperatively, and hepatic resection can be done in accordance with the radioimmunologic diagnosis. The effect of surgical as well as medical therapy on liver metastases could be checked and followed most carefully.

SUMMARY

Percutaneous transhepatic catheterization of the portal vein along with the catheterization of the aorta and the vena cava was performed in six patients, one of whom had hypoglycemic attacks due to Whipple's triad. Blood samples from different branches in the different vessel systems were withdrawn for radioimmunologic determination of insulin. By this method, preoperative localization

of the insulin producing pancreatic islet cell tumor was successfully performed. Multiple tumors as well as liver metastases were preoperatively excluded. Recatheterization and blood sampling for radioimmunologic determination of insulin was performed postoperatively to verify the radicality of the operation. Insulin concentrations from the hypoglycemic patients were compared with those of the patients without insulinoma and found to be significantly higher. The procedure is proposed as a useful method for localizing all types of gastrointestinal hormone producing primary or secondary tumors in which a method for hormone determination is available. The postoperative investigation is useful as a check of the operation performed and as a follow-up examination for the early diagnosis of recurrence.

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